B2

then expanding the selected cells to [clinically relevant numbers] in excess of 1 x 10^{10} cells.

B3

40. (Amended) The method of claim 38, wherein after activation, the cells are grown in the presence of [the protein activating agents are] anti-CD28 monoclonal antibodies and interferon-γ.

155. (Twice Amended) The method of claim 36, wherein the cells are expanded to an excess of [10^{9}] 10^{10} cells in a volume of a liter or less.

B4

156.(Amended) The method of claim 36, wherein the cells are expanded to an excess of 10^{10} cells in a volume of 500 mls or less.

157. (Amended) The method of claim 36, wherein the expansion of cells occurs under conditions that produce high cell density, wherein the density is greater than 10^{8} cells/ml.

REMARKS

A check for the fee for a three month extension of time accompanies this response. Any fee that may be due in connection with this application may be charged to Deposit Account No. Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 36-40 and 154-167 are presently pending. Claims 36-38, 40 and 155-57 are amended to address minor language inconsistencies and to emphasize the definitional basis for "clinically relevant numbers." Claims 158-167 are added to conform claims to the election of species requirement. Basis for amendment of the claims may be found in the instant application as originally filed, and, also in the parent application (see discussion below). The obvious typographical error on page 1 of the specification noted by the Examiner is corrected by amendment herein. Additional obvious typographical errors are also corrected. No new matter is added.

The traversal of the requirement for election of species is maintained and reconsideration thereof is again sought. Applicant reserves the right to file divisional applications to any cancelled subject matter.

SUBSTITUTE DECLARATION

A substitute DECLARATION has been prepared and will be submitted under separate cover.

BASIS IN PARENT APPLICATION FOR CLAIMS IN THIS APPLICATION AND DEFINITIONS OF EFFECTOR AND REGULATORY CELLS

It is respectfully submitted that pending claims do find basis in the parent application. The specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). The test for new matter is whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02). Furthermore, the **subject matter of the claim need not be described literally (i.e., using the same terms or inhaec verba**) in order for the disclosure to satisfy the description requirement.

The specification as originally filed conveys with reasonable clarity disclosure that supports all of the pending claims and the claims of this application as originally filed.

In the parent application, U.S. provisional application Serial No. 60/044,693 (converted to a provisional from application Serial No. 08/506,608) claim 1 recites:

1. A method for generating autologous effector immune cells, the method comprising:

collecting leukocyte containing material from a mammal; and
exposing the leukocyte containing material to mitogenic monoclonal antibodies to induce *in vitro* cell proliferation sufficient for infusion into the mammal for use in an immunotherapy treatment, wherein the *in vitro* cell proliferation is produced without the use of exogenous interleukin-2.

Claim 15 recites that cells are produced by first treating them to alter their cytokine production profile; and are then proliferation to numbers sufficient for infusion into a mammal for use in the adoptive immunotherapy.

Claims 11 recites that the leukocyte containing material is treated with mon or more cell-surface protein specific monoclonal antibodies; claims 7-10 and 17-23 recite that the cells are treated to become Th1 or Th2 cells

Claims 14 and 27 of that case recites that the cells are proliferated to "an excess of 1 x 10^{10} cells."

Claim 7 recites that the cells are Th1-like or Th2-like cells, thereby indicating that as originally filed, what are now called regulatory cells were contemplated to be within the scope of the original claims and to be separately claimed.

The parent application is directed to methods for the production of high concentrations and amounts of homogeneous compositions of immune cells, including Th1, Th2, and also LAK, CTL and TIL cells, in the absence of exogenously added IL-2. In the parent application, the term "effector" cell was used to encompass all types of regulatory cells. Dependent claims separated out the Th1 and Th2 cells from the generic type. Claim 1 generically encompassed all types of T cells.

In the instant application, the nomenclature, **not** the intended scope of the claims, was modified so that the generic language refers to what was called effector cells in the parent application as "immune cells" Compare claim 1 as originally in the instant case with claim 1 of the parent case. The language "effector" is changed to immune cell. Further, two classes of cells were defined: regulatory immune cells, which are clearly defined (as discussed below) to include Th1 and Th2 cells, which can be identified by their distinct cytokine profiles and which act on other cells; and effector immune cells, which are defined as the LAK, CTL, MAK and TIL type cells.

The parent specification states at page 7, line 16. that effector cells include Th1, Th2-like cells. The specification describes Th1 and Th2 cells at page 8, lines 27, page 9, line 3, and page 9, lines 20-24; and states at page 9, lines 25-28:

> Accordingly, it is desirable to have the ability to produce large quantities of autologous Th1 T-cells in disease states where a Th2 cytokine profile predominates (infectious disease) and Th2 T-cells in a TH1-dominant disease (chronic inflammation and autoimmune disease).

Methods for differentiation of immune cells into Th1 or Th2 cells are described at page 11, lines 11-19.

In the parent specification, production of clinically relevant numbers of cells Th1 cells (and also Th2 cells) is described at page 7, lines 6-25. At page 8, lines 25,- page 9, line 3, the parent specification states that CD4+ cells can be subdivided into TH1 cells and Th2 cells. At page 9, line 25, - page 10, line the parent application states that it is desirable to produce large quantities of Th1 T-cells in disease states where a Th2 cytokine profile predominates, such as in infectious diseases, and to produce large quantities of Th1 cells in diseases in which Th1 cells predominate, such as chronic inflammation and autoimmune disease. The parent application describes large quantities as an "excess of 10^{10} cells (see page 6,

line 26, page 7, lines 13-15). At page 10, lines 5 = 7, the parent application states that:

> The present invention includes a process that enables the production of large quantities of immune cells, such as Th1 and Th2 cells, for use in ACI of human disease.

The process for preparing these cells is described on page 10, line 14, - page 14, line 20). It is exemplified in Example 1, which shows that non-specific $CD4^+$ and $CD8^+$ cells can be expanded to "clinically relevant numbers" (page 30, lines 9-10). Greater than 10^{10} cells $CD4^+$ and $CD8^+$ were shown to be produced. Example 2 (see page 34 of the parent application) shows preparation of clinically relevant numbers of virally purged (HIV-) $CD4^+$ Th1 cells and claims 28 and 29 are directed to virally purged CD4+ cells, and claim 29 recites that the cells are Th1 cells.

In particular, Example 2 describes expansion of HIV- $CD4^+$ cells in the absence of IL-2. Example 2 describes the isolation of $CD4^+$ cells from an HIV patient, activation of the cells with immobilized and CD3 mAB in the presence of IFN-γ, selection for HIV- cells, and then expansion as in Example to produce more than 10^{10} cells. Example 3 shows selection and expansion of CTL cells, in the absence of IL-2, to amounts grater than 10^{10}; and Example 4 shows activation and expansion of HIV- $CD4^+$ cells in the absence of IL-2 to produce greater and 10^{10} Th2 $CD4^+$ cells.

The scope of the claims and subject matter of the claims as originally filed and as filed in the instant cased are the same. The definitions were slightly modified in the instant case; but it is clear from the context that broad claims to the general method of inducing activation and proliferation using mitogenic antibodies in the absence of exogenous IL-2 (see claims 1-14), and claims in which the cells are caused to differentiate into Th1 or Th2 (or Th1-like or Th2-like) populations of cells prior to proliferation (claims 15-27) cover the same methods.

The parent application states, starting at page 6, line 23, that:

> use of ACI protocols will require technology that enables: the generation of homogeneous populations of immune effector cells [*i.e.*, cells that include TILs, LAKs, CTLs, Th1, Th2 cells]; the consistent growth of effector cells to clinically relevant dosages (*i.e.*, greater than 10^{10} cells) without the use of IL-2; . . . and the ability to reinfuse the cells without the need for systemic infusion of IL-2. Furthermore additional *in vitro* differentiation strategies are need to broaden the types of cells available for ACI protocols.

The present invention addresses each of these requirements, disclosing a method to differentiate Th1 or TH2 cells *in vitro* and grow these cells to clinically relevant numbers without the use of IL-2.

The parent application also makes it abundantly clear that the prior art all disadvantageously (see page 6, line 5, - page 7, line 5)

> include the use of IL-2 as a growth stimulant, requiring Il-2 also to be infused concomitant with the cells . . .. With the exception of the A-LAK protocol, no prior art method attempts to purify the effector cells to generate homogeneous cell populations.. . .
>
> Clinical testing of ACI protocols in cancer has [been] greatly curtailed . . . because the potential efficacy of LAK and TIL therapies has been overshadowed by the substantial toxicity of the treatments. The toxicity is attributed to the administration of systemic IL-2 . . . [that] is necessary in these protocols because lymphocytes differentiated or grown in IL-2 die within 48 hours of IL-2 withdrawal.
>
> Therefore, expanded use of ACI protocols will require technology that enables: the generation of homogeneous populations of effector immune cells; the consistent growth of effector cells to clinically relevant dosages *(i.e., greater than 10^{10}* **cells) without the use of IL-2** . . ..
>
> The present invention addresses each of these requirements disclosing a method to differentiate Th1 or Th2 cells *in vitro* and grow these cells to clinically relevant numbers without the use of IL-2.

This provides clear unequivocal basis for the pending claims in the present application.

The instant application has been rewritten for clarity, not to add new matter to the original claims, and to provide additional examples of applications of the technology. To distinguish between differentiation of cells to produce LAKs, TILs and CTLs, from differentiation to produce Th1, Th2 and Th3 cells and subcategories thereof, different nomenclature has been adopted. The same cells are encompassed by the claims; their names are different. Changing the names of claimed subject matter does not add new matter if the substance remains substantially the same.

Finally, as discussed below, whether or not basis in the parent application is accorded to some or all of the instant claims is not relevant to the patentability of the instant claims over the cited art and art of record. None of the cited references, singly or in any combination thereof, teaches or suggests methods for preparation of compositions containing predominantly one type of T-cell, nor methods for expansion of such cells in the absence of IL-2.

Prefatory remarks

IMMUNOLOGICAL PARADIGM

Blood contains two main types of regulatory immune cells designated Th1 and Th2 cells (see, *e.g.*, Cherwinski *et al.* (1987) *J Exp Med 166*:1229-44; and Mosmann *et al.* (1986) *J Immunol 136*:2348-2357). Alteration of the balance of these cells leads to devastating disorders such as cancer, autoimmune, infectious and allergic diseases, spontaneous abortion and transplant rejection.

NORMAL IMMUNE SYSTEM

In healthy adults Th1 and Th2 cells are maintained in a carefully regulated balance. When challenged with a virus, the immune system balance changes in favor of Th1 cells. After the virus is eliminated, Th2 cells increase and the immune system returns to balance. Parasitic infections are eliminated by an increase in Th2 cells. An increase in Th1 cells after elimination of the parasite returns the system to normal balance.

CANCER AND INFECTIOUS DISEASE

Patients with advanced cancer or afflicted with infectious diseases (such as AIDS, hepatitis B or C, herpes) have a regulatory immune imbalance in favor of Th2 cells. The excess Th2 cells chronically suppress the body's ability to mount an immune response to eliminate the tumor or virus. Excess Th2 cells are also found in patients with severe allergic diseases such as asthma and in patients with Lupus. Th1 cells are also lost with aging increasing susceptibility to cancer and infectious diseases, cancer, hepatitis C, AIDS and others.

AUTOIMMUNE DISEASE

Patients with autoimmune diseases (such as rheumatoid arthritis, multiple sclerosis, diabetes and inflammatory bowel disease, have a regulatory immune cell imbalance in favor of Th1 cells. The excess Th1 cells mediate a chronic inflammatory condition that destroys the body's own tissues. For example, excess Th1 cells are also responsible for rejecting organ transplants and causing spontaneous abortion

TREATMENTS

The instant application provides immunotherapeutic treatments that act to reduce the magnitude of a Th1/Th2 regulatory cell imbalance have been proven to be therapeutic for many diseases. The technology provided by the instant application is capable of correcting even the most severe Th1/Th2 regulatory cell imbalances, providing hope for millions of patients with devastating diseases for which there currently are no cures or adequate treatments.

This application is directed to methods for generating substantially homogeneous compositions of cells that contain a high concentration of one population of immune cells, where expansion is effected in the absence of exogenous IL-2, and also to methods for treatment of diseases by altering immune

balance using such compositions. The claims in this application are directed to the methods of producing the such substantially homogenous compositions.

As stated at page 12 of the specification:

> Methods of use of regulatory immune cells in autologous cell therapy (ACT) protocols to treat and prevent human disease are provided. The ACT protocols designed to alter the immunoregulatory balance of a patient in order to treat diseases where imbalances in regulatory cells exist. In particular, ACT protocols designed to alter the immunoregulatory balance of a patient in order to treat diseases where imbalances in regulatory cells exist are provided.

There are two major types of regulatory immune cells (formerly under the umbrella of effector cells, but under current terminology **and as defined in the specification)**: Th1 cells, which promote an inflammatory response, and Th2 cells, which act to suppress an inflammatory response. These cells refer to populations of cells in which one cell type predominates; the cell type is defined by its cytokine profile.

The immune system normally maintains these cells in a carefully regulated balance. Imbalances in these regulatory cells are characteristic of many incurable diseases, such as metastatic cancers, autoimmune, allergic and infectious diseases. For example, cancer patients have an excess of Th2 regulatory cells, which suppress the immune system; whereas autoimmune disease patients have an excess of Th1 regulatory cells, which promote an inflammatory response. The methods herein, provide a means to produce high concentrations of one type of immune cell by collecting lymphoid cells, *differentiating* them into substantially one type of immune cell, and then stimulating them to proliferate to high densities. For treatment, the cells are reinfused into the patient to restore immune balance. The type of cell selected depends upon the disease being treated. All of these aspects are described and disclosed in the parent application U.S. application Serial No. 08/506,668, converted to U.S. provisional application Serial No. 60/044,693.

Traverse of the election of species requirement

What the Examiner has characterized as "species" are dependent claims directed specific embodiments of the invention. The invention lies in the concept of altering immune balance by administering populations of cells that contain predominantly one type of immune cell in a sufficient concentration to alter immune balance in the recipient using a homogenous population of cells; in methods for production of cells for use in the methods, and in the resulting compositions of cells. In this case the invention lies in the method for expanding $CD4^+$ cells from HIV patients to produce clinically relevant numbers of virally purged cell. Methods for preparing compositions for administration are provided as are methods using the compositions, which have also been claimed.

The claims in the instant application are directed to methods for preparing compositions containing high amounts (and densities) of HIV- $CD4^+$ cells; dependent claims specify that the cells are predominantly Th1 cells, and specify the manner in which Th1 cells are produced.

Claim 36 is directed to a method for producing clinically relevant numbers of HIV- $CD4^+$ cells; claim 37 specifies that the cells are treated to produce predominantly Th1 cells prior to expansion, and claim 40 specifies the reagents used to produce predominantly Th1 cells. If this election of species is maintained, claims 36, 37, 38 and 40 will be required to be filed in separate applications. It also is noted that as originally filed, a restriction requirement issued dividing the case into five groups. In reliance upon that requirement, four divisional application have been filed. In each of these cases, including this case, further election requirements have been imposed resulting in division of the case into what will be (if the requirements are maintained) 25 or more applications. This application, which was filed in reliance upon the original restriction requirement dividing the

original claims into five groups, has now been divided into at least 5 additional applications. Each of the divisionals has been similarly divided.

As discussed above, the claims in all cases relate to the same generic concept of producing high concentrations and amounts of homogeneous compositions of cells for infusion in the absence of IL-2 into mammals in order to alter or restore immune system balance. With the exception of original claim 1 and claim 36, which is directed to a method for generating virally purged $CD4^+$ cells, and certain claims dependent on claims 1 and 36, the methods involve obtaining immune cells, treating them so that they differentiate into one type of immune cell, and then treating them so that they proliferate into a high number of cells. Dependent claims specify ways of differentiating them, ways of proliferating them, the products of the differentiation/proliferation methods, and use of the products for treatment. This subject matter does not warrant 25 patent applications. Certainly the claims in the instant case, do not belong in five or six separate applications.

The Office is reminded that as between the presently pending claims in this case and the other co-pending cases and other divisionals that will be filed based upon the parent application U.S. application Serial No. 08/506,608, obviousness-type double patenting cannot be held. All of these cases and the cases that will be filed are filed in accord with restriction requirements as set forth by the Office. In no case should a rejection for obviousness-type double patenting be made (*i.e.*, if a separate application with claim 40 is filed, obviousness-type double patenting cannot be held as between that case and any claims in this case).

See, MPEP 804.01, which states:

> 35 U.S.C.121, third sentence, provides that wherein the Office requires restriction, the patent of either the parent or any divisional application thereof conforming to the requirement cannot be used as a reference against the other. This apparent nullification of double patenting as ground of rejection or invalidity in such cases imposes a

heavy burden on the Office to guard against erroneous requirements for restriction where the claims define essentially the same inventions in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

THE REJECTION OF CLAIM 37 AND 39 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 37 and 39 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing new matter. The Examiner urges that there is no "support in the specification for recitation of "isolating mononuclear cells" in claims 36 and 37. This rejection is respectfully traversed.

It is respectfully submitted that there is basis in this application and in the parent application for the step of isolating mononuclear cells. Attention is directed, for example, to Example 2 (in this case; see, also Example 2 in the parent application), which states:

> **A. Collecting mononuclear cells**
> Mononuclear cells from normal donors were obtained from source leukocyte packs (Interstate Blood Bank, Inc.).. . .

See, also, page 13, lines 1-19:

> The methods involve collecting **peripheral blood mononuclear cells from a patient** and then expanding the cells by appropriate activation and then mitogenic stimulation with a cell surface specific proteins or proteins under conditions whereby clinically relevant numbers of the expanded cell type are produced [typically 10^9, preferably 10^{10}, more preferably 10^{11}, or more depending upon the cell type and ultimate application]. If the collected cells are not differentiated *in vivo* or require further differentiation, then following collection and prior to expansion, the method includes activating and causing differentiation of the cells *ex vivo* under conditions whereby at least some of the cells differentiate into regulatory or effector cells or other cell types. The resulting cells are then reinfused into the donor to effect treatment. The desired cells may be purified prior to reinfusion to provided a more homogeneous population.
>
> Where required, **differentiation of mononuclear cells** is effected by activating the cells with a mitogen in the presence of the appropriate array of

> cytokines. This activation can be achieved by use of agents, such as cytokines or mitogens or other growth promoting agents under environmental conditions conducive to development of a particular phenotype. For example, if the cells are activated in the presence of IFN-γ, Th1 cell differentiation will be produced. If they are activated in the presence of IL-4, then Th2 cell differentiation will be produced.

See page 28, lines 10-30, which state:

> **1. Collecting mononuclear cells**
>
> Mononuclear cells (i.e., lymphocytes and monocytes) can be obtained from a variety of sources, including, but not limited to, peripheral blood, lymphoid tissue, biopsy tissue or from body cavity lavage procedures. Preferably, the cells are obtained by simple venipuncture (50-500 ml). When larger numbers of cells are required, they may be obtained by a lymphapheresis procedure. The mononuclear cells can be purified from the blood using Ficoll-Hypaque density gradient centrifugation or any other suitable method.

See also, page 14, lines 7 and 30, page 29, line 20, and elsewhere throughout the specification. See, also, Example 1, page 30 line 13, Example 2, page 34, line 7, of the parent application.

REJECTION OF CLAIMS 37 and 39 UNDER 35 U.S.C. § 103(a)

Claims 37 and 39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Babbitt *et al.* (U.S. Patent No. 5,766,920) in view of Carew (U.S. Patent No. 5,123,901) and Nabel *et al.* because Babbitt *et al.* teaches methods for producing Th1 cells by removing patient mononuclear cells are removed and activating and expanding them in the presence of IFN-γ enriched supernatant and OKT3 (anti-CD3 antibody) to produce Th1 cells and then reinfusing the cells to treat HIV. Babbitt *et al.* does not teach that HIV negative Th1 cells are selected after activation; Nabel *et al.* teaches that T cell activation results in production of HIV virus in latently infected T cells, and Carew teaches that HIV positive T cells can be removed from blood by treatment with immunoreactive beads coated with a reagent that binds HIV (see Abstract and column 2, last paragraph). The Examiner

concludes it would have been obvious to one of ordinary skill in the art to have to have created the claimed invention" because Babbitt *et al.* is alleged to teach methods for producing Th1 cells from HIV infected patients, where patient mononuclear cells are removed, activated and expanded *in vitro*, Nabel teaches that T cell activation results in production of HIV virus in latently infected T cells and Carew is alleged to teach that HIV positive T cells can be removed from blood or a fluid containing treatment with immunoreactive beads coated with a reagent that binds to HIV. The Examiner urges that one of ordinary skill in the art would have been motivated to do the aforementioned because Carew teaches that HIV infected T cells should be removed from blood products that are administered to humans (see abstract). This rejection is respectfully traversed.

The Claims

Claim 36 is directed to a method of producing virally purged CD4+ cells by isolating mononuclear cells from a patient infected with HIV, activating the cells by contacting the cells with mitogenic antibodies, selecting CD4+ cells that are HIV- after activation, and then expanding the selected cells to clinically relevant numbers in the absence of interleukin-2 (IL-2). Claim 37 specifies that the cells are activated under conditions that produce Th1 cells. Claim 38 is directed to the method where the selecting step prior to expanding the selected cells, a plurality of aliquots of the cells are grown in the presence of mitogenic agents, and HIV- cells are selected and then expanded, and claim 40 recites that the cells are first treated to produce Th1 cells. Claim 39 specifies that the reagents used to activate the cells. Claims 154 recites that the cells are expanded in a hollow fiber bioreactor, and claims 155-157 recite the resulting volume and/or density.

Teachings of the cited references and differences from the instant claims

Babbitt *et al.*

Babbitt *et al.* is directed to a method for producing immunoreactive cells by contacting a first sample of mononuclear cells with OKT3 at or below 37° C to "produce an OKT-3-derived culture supernatant (T3CS)", removing the T3CS from the mononuclear cells; optionally supplementing the T3CS with additional OKT3 to produce a concentration of at least 0.1 ng/ml of OKT3, and then contacting a second sample of mononuclear cells with the T3CS to produce immunoreactive cells. The T3CS is conditioned medium that contains autologous cytokines to promote differentiation of Th1 cells.

Hence Babbitt *et al.* is directed to a method for producing activated cells. Any teachings regarding expansion of the cells contemplates using IL-2 to effect expansion (see column 18, lines 7 -20). As exemplified, expansion only produces 10^9 cells, not the 10^{10} cells contemplated in the instant application. Thus, Babbitt *et al.* does not teach a method for producing clinically relevant numbers of cells in which expansion is effected in the absence of exogenous IL-2. Babbitt *et al.* does not teach or suggest a step of expanding the cells to clinically relevant numbers in the absence of IL-2.

In addition, Babbitt *et al.* does not contemplate production of virally purged cells nor preparation of clinically relevant numbers of cells (an excess of 10^{10} cells) for reinfusion of the cells. Babbitt *et al.* (col. 7) states that:

> Mononuclear cells taken from a patient afflicted with a complex chronic viral disease may also be processed according to the invention to yield immunoreactive cells which can then be returned to the patient to augment the patient's immune response to the pathogen. Patients infected with pathogenic viruses, . . . and HIV (HIV-1 and HIV-2) may be treated in this manner.

Thus, Babbitt *et al.* contemplates activation of cells and reinfusion of the cells to augment an immune response to the pathogen.

Babbitt *et al.* does not teach the steps of activating mononuclear cells by contacting the cells with mitogenic antibodies, and selecting CD4+ cells that are HIV- after activation. The method of Babbitt *et al.* does not use mitogenic antibodies for activation, but rather uses a supernatant and a single monoclonal antibody. Further, the method does not include a step of selecting for HIV- $CD4^+$ cells after activation. Furthermore, Babbitt *et al.* does not suggest the step of expanding the selected $CD4^+$ cells that are HIV- to clinically relevant numbers in the absence of interleukin-2 (IL-2).

Carew

Carew does not cure these deficiencies. Carew is directed to a method for removing pathogenic agents from body fluids. The body fluid is perfused into a mixing coil with paramagnetic beads that selectively bind to the pathogenic agent; and the beads are then separated from the fluid. In one embodiment blood is treated to remove infected T-lymphocytes by continuously perfusing the blood through the mixing coil using a peristaltic pump. Hence the method of Carew involves filtration of the blood of an individual.

Carew does not teach or suggest use of its method in combination with adoptive immunotherapy protocols in which selected cells are activated and then expanded. Carew does not teach or suggest a step of expanding the cells to clinically relevant numbers in the absence of IL-2, an element missing from the teachings of Babbitt *et al.* N Hence Carew does not cure the deficiencies in the teachings of Babbitt *et al.*

Nabel *et al.*

Nabel *et al.* does not cure the deficiencies in the teachings of Babbitt *et al.* and Carew. Nabel *et al.* teaches that human immunodeficiency virus (HIV) production from latently infected T lymphocytes can be induced with compounds that activate the cells to secrete lymphokines. Other than a possible suggestion

that activation of cells by the method of Babbitt *et al.* results in production of HIV from infected lymphocytes in the mononuclear samples, Nabel *et al.* has no relevance to the instant claims, which are directed to methods for preparing compositions of virally purged cells.

Nabel *et al.* provides no teachings or suggestions directed to methods for preparing HIV- compositions of cells. Nabel *et al.* does not teach or suggest a step of expanding the cells to clinically relevant numbers in the absence of IL-2, an element missing from the teachings of Babbitt *et al.*

The Examiner has failed to set forth a case of *prima facie* obviousness

(1) Relevant law

In order to set forth a prima facie case of obviousness under 35 U.S.C. § 103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (BPAI 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)).

(2) Analysis

There would not have been motivation to have combined the teachings of Babbitt *et al.* with those of Carew *et al.* and Nabel

Babbitt *et al.* is directed to a method for activating mononuclear cells; Carew is directed to a perfusion-based method of removing pathogens from body fluids, and Nabel *et al.* teaches that compounds that activate lymphocytes can induce production of HIV from latently infected cells. Each of the references is directed to a different method. Carew is an *in vivo* method and Babbitt *et al.* is an *ex vivo* method. Nabel merely provides an observation.

There are no teachings in any of the reference that suggest combination thereof. More significantly, the combination of teachings of the references does not result in the instantly claimed methods.

The combination of references does not result in the claimed subject matter

The combination of Babbitt *et al.* and Nabel would suggest that the activation method of Babbitt *et al.* might result in HIV production in latently infected cells. Combining these teachings with those of Carew at most would suggest a way to remove the induced HIV. As noted, however, the method of Carew is performed *in vivo*, whereas Babbitt *et al.* is performed *ex vivo* on a small samples of cells. Notwithstanding these deficiencies, none of the references singly or in combination, suggests activating $CD4^+$ cells, selecting HIV- cells from among these, and then after activation expanding the cells to in excess of 10^{10} cells in the absence of IL-2. Therefore, the combination of teachings of the references does not result in the instantly claimed methods.

The rejection over Babbitt *et al.* in view of Carew and Nabel *et al.* is based on the improper use of hindsight.

The disclosure of the applicant cannot be used to hunt through the prior art for the claimed elements and then combine them as claimed. In re Laskowski, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art

reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

It appears that the Examiner has combined the teachings of the prior art with those of the instant application. It is the instant application that suggests altering immune balance by administering compositions containing clinically relevant numbers of cells, particularly clinically relevant numbers of either Th1 or Th2 cells; none of the cited references provide the suggestion for preparation of clinically relevant numbers of cells. Rather it is the instant application that provides such teaching. Furthermore, selection of divergent references, such as Babbitt *et al.*, Carew and Nabel *et al.* from among the prior art in this field and then combining selected teachings from each references, relies on the instant application as a guide. There is nothing in Babbitt *et al.* that would have led the skilled artisan to consider selecting for HIV- cells. Babbitt *et al.* teaches activating cells as a means to "augment" the immune response and thereby treat viral infection; Babbitt *et al.* does not suggest alteration of the immune response by administration of in excess of 10^{10} cells. The method of Carew is an *in vivo* perfusion method in which a patient's blood is treated to remove viral particles. Carew does not suggest treating samples of blood. Babbitt *et al.* teaches removal of small samples of monocytes, and using one sample to generate the T3CS and then contacting another with the T3CS to activate cells; there is no suggestion in Carew for treating the samples used by Babbitt *et al.* to produce the T3CS or that are contacted with the T3CS with coated paramagnetic beads. Furthermore, Nabel does not suggest activating cells as a means to induce viral expression for treatment of any sort.

Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

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In view of the above remarks and the amendments and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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